## REMARKS

This is being filed in response to the Office Action dated February 7, 2005. Claims 1-26 are pending in the application. Claims 1-7, 9-13, 15, 23, 24 and 26 were withdrawn from consideration. Thus, claims 8, 14, 16-22 and 25 are currently under examination.

Claims 8 and 14 have been amended to depend from claims 16 and 25, respectively. Claim 8 has been amended to recite "reverse-immortalized hepatocytes" rather than "functional hepatocytes" for consistency with the independent claim. Likewise, claim 14 has been amended to recite "immortalized hepatocyte" rather than "functional hepatocytes" for consistency with the independent claim. Claim 25 has been amended for clarity, as helpfully suggested by the Examiner. No new matter is added. Applicants earnestly submit that claims 8, 14 and 25 are in proper form for allowance.

**35 U.S.C. §102(b) and 35 U.S.C. §103(a)**

Turning to the merits of the application, the Office Action rejects claims 8, 14 and 25 under 35 U.S.C. §102(b) as anticipated by Yurasov *et al.* (1997) *Blood* 89(5):1800-1810 ("Yurasov"), or in the alternative, under 35 U.S.C. §103(a) as obvious over Yurasov.

The Office Action alleges that Yurasov teaches the transduction of hepatocytes with vectors that do not contain an immortalization gene, and that the cells are "indistinguishable" from the claimed cells, differing only in the method of manufacture. This is not correct. The claimed cells are transformed with vectors that contain an immortalization gene flanked by recombinase target sites. Upon excision, the recombinase target sites remain in the cell (note that claim 16 recites "comprising two recombinase sites" and claim 25 refers back to claim 16). Thus, the cells are genotypically different from the cells of Yurasov. As Yurasov lacks an element of the claim, it cannot be anticipatory. Withdrawal of the rejection under 35 U.S.C. §102(b) is respectfully requested.

Yurasov also does not render the claims obvious. Yurasov does not teach or suggest a cell undergoing reversible immortalization. Nowhere does Yurasov teach or suggest making a cell immortal, expanding such an immortalized cell population and then reversing the immortalization. As for the Office Action's assertion that the cells of Yurasov and the claims are "indistinguishable," applicants note that it would not be obvious to include recombinase

sites in Yurasov's vectors if they were not to be used for something. Yurasov neither teaches nor suggests such a use. Withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

The Office Action further rejects claims 8, 14 and 25 under 35 U.S.C. §102(b) as anticipated by Adams *et al.* (1992) *Proc. Nat'l. Acad. Sci. USA* 89(19):8981-8985 ("Adams"), or in the alternative, under 35 U.S.C. §103(a) as obvious over Adams.

Similarly to the discussion for Yurasov above, the Office Action alleges that Adams teaches the transduction of hepatocytes with vectors that do not contain an immortalization gene, and that the cells are "indistinguishable" from the claimed cells, differing only in the method of manufacture. This is not correct for Adams either.

The claimed cells are transformed with vectors that contain an immortalization gene flanked by recombinase target sites. Upon excision, the recombinase target sites remain in the cell (note that claim 16 recites "comprising two recombinase sites" and claim 25 refers back to claim 16). Thus, the cells are genotypically different from the cells of Adams. As Adams lacks an element of the claim, it cannot be anticipatory. Withdrawal of the rejection under 35 U.S.C. §102(b) is respectfully requested.

Adams also does not render the claims obvious. Nowhere does Adams teach or suggest making a cell immortal, expanding such an immortalized cell population and then reversing the immortalization. As for the Office Action's assertion that the cells of Adams and the claimed cells are "indistinguishable," applicants note that it would not be obvious to include recombinase sites in Adam's vectors as Adams states that the purpose of the study was "to assess whether methods for hepatocellular harvest, cultivation and retroviral transduction of primary hepatocytes that have been used in animals were applicable to humans." (Adams, p. 8984, first paragraph under "Discussion"). Adams looked at harvesting and culturing primary hepatocytes as well as the ability to transducer them with amphotropic and xenotropic vectors. Adams does not teach or suggest using a reversible expression system or recombinase sites for expressing and removing genes. Withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

**35 U.S.C. §103(a)**

The Office Action also rejects claims 16-22 under 35 U.S.C. §103(a) as obvious over U.S. Patent No. 5,629,159 to Anderson ("Anderson") in view of Nakamura *et al.* (1996) *Transplant* 63:1541-1547 ("Nakamura"), and Adams or Yurasov.

Anderson teaches immortalization of cells using a vector carrying an immortalization gene and then physically removing the immortalization gene from transduced cells to "disimmortalize" them. As the Examiner frankly admits, Anderson does not teach the transduction of hepatocytes (Office Action of February 7, 2005, page 7). The Office Action relied on Nakamura to establish the desirability and feasibility to use conditionally immortalized hepatocytes for treating liver disease. Nakamura, however, teaches conditionally immortalized cells. That is, cells that proliferate at 33°C (*i.e.* outside of the body), but do not proliferate at 37-39°C (*i.e.*, inside the body). At no time does Nakamura teach or suggest that the immortalization gene could be physically removed from the cells as taught by Anderson. This has significance. In Nakamura's study, rats were treated with cells that contained an immortalization gene. Whether there was leaky expression of the gene is completely unknown. Anderson teaches treatment with cells in which such a gene is *physically removed* recognizing that treatment of patients with cells containing oncogenes is unsuitable for transplantation due to the "undesirability of introducing oncogenes into a patient" (col. 1, lines 23-25). Thus, Anderson teaches away from introducing cells into a patient wherein the cells contain an oncogene. Therefore, it is against the operating principal of Anderson to use cells containing an oncogene (as taught by Nakamura). Although Nakamura teaches that the oncogene is temperature-sensitive, the implication of Anderson is that the introduction of an oncogene into a patient is simply too risky to be desirable. Without more, the Office Action is merely stating that it would be obvious to try to use the vectors of Anderson in liver cells, although, such is never an acceptable standard for making a *prima facie* case for obviousness.

Adams or Yurasov are cited to supplement the Office Actions assertion that hepatocytes could be transformed with a DNA construct. However, Adams clearly teaches that there would be no reasonable expectation of success that the transformation of hepatocytes is efficient enough for use:

> The present work suggests that data from transduction of rodent hepatocytes with amphotropic vectors may not accurately predict the efficiency of transduction of human cells.... The data in this report demonstrate that the efficiency of transduction with amphotropic vectors is sufficient to provide a detectable marker in this clinical trial. Significantly higher transduction efficiencies will be required, however, before somatic gene therapy can be proposed with confidence.
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> Adams, p. 8984 last paragraph to p. 8985

Thus, contrary to the Office Action's assertion, Adams does not provide a reasonable expectation of success that a particular vector (from Anderson) would be successful for transduction of hepatocytes. The difficulty encountered by Adams suggests that there is no reasonable expectation of feasibility or success that Adams experiments would work using Anderson's vectors.

Similarly, Yurasov teaches transduction of cells with constructs that do not contain an immortalization gene. It is completely unknown how the introduction of a vector containing an immortalization gene would have affected Yurasov's study. What is unknown cannot be obvious.

Applicants earnestly submit that the claims are allowable over the hypothetical combination of Adams, Nakamura in view of Adams or Yurasov. Withdrawal of the rejection is respectfully requested.

Applicants respectfully submit that the claims are in condition for allowance, which action is respectfully requested.

Respectfully submitted,

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